

Applicant : Vincent P. Stan  
Serial No. :  
Filed : HEREWITH  
Page : 15

Attorney's Docket No.: 11926-015002

### REMARKS

The amendment to the specification is made solely to insert the Sequence Listing and SEQ ID NOS. into the specification. No new matter is introduced. The accompanying declaration by the inventor confirms that the sequences in the Sequence Listing are the same as those incorporated by reference into the original specification by providing the GenBank® Accession Number for each sequence. A signed declaration will be filed under separate cover.

Applicant requests that claims 17-49 be examined together without restriction. Each of SEQ ID NOS:6, 7, and 8 relate to the human thymidylate synthetase gene. SEQ ID NO:6 corresponds to the coding region. SEQ ID NO:7 corresponds to the promoter region. SEQ ID NO:9 corresponds to the exons. Three SEQ ID NOS are required even though only one gene is referenced because the original specification identified the sequences by providing three GenBank® Accession Numbers.

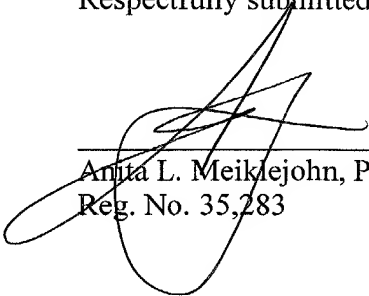
Each of the nucleotides specified in the claims represents a single nucleotide polymorphism in the human thymidylate synthetase gene.

Attached is a marked-up version of the changes being made by the current amendment.

Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 24 Sept 2001

  
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Applicant : Vincent P. Stanton  
Serial No. :  
Filed : HEREWITH  
Page : 16

Attorney's Docket No.: 11926-015002

**Version with markings to show changes made**

**In the specification:**

The paragraph beginning at page 1, line 8, has been amended as follows:

This application is a divisional of U.S. Application Serial No. 09/658,659, filed September 8, 2000, which is a CIP of Stanton, U.S. Application serial No. 09/596,033, filed June 15, 2000 entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application 09/357,743, filed July 20, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE which is a CIP of Stanton, U.S. Application Serial No. 09/357,024, filed July 19, 1999, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which claims the benefit of Stanton, U.S. Provisional Application 60/093,484, filed July 20, 1998, entitled GENE SEQUENCE VARIACNES IN GENES RELATED TO FOLATE METABOLISM HAVING UTILITY IN DETERMINING THE TREATMENT OF DISEASE, which are all hereby incorporated by reference in their entireties including drawings and tables.

Table 10 beginning at page 171 has been amended as follows:

**Table 10**

**Variance Table**

Hugo	GID	OMIM ID	VGX Symbol	Description
Variance Start	Variance			
U73338	U73338	156570	GEN-69	Methionine
Synthase (SEQ ID NO:1)				
	194	(-201)C>G		5'
	284	(-111)C>T		5'
	1136	742G>A		V248M
	1252	858C>T		Silent

Attorney's Docket No.: 11926-015002

	1334		940G>A	D314N
	1699		1305T>C	Silent
	3150		2756A>G	D919G
	3207		2813G>T	S938I
	3209		2815G>C	G939R
	5444		5050C>A	3'
	5551		5157G>A	3'
	5573		5179C>T	3'
	5659		5265T>C	3'
	5678		5284T>C	3'
	5874		5480C>T	3'
	5934		5540A>G	3'
D78586	D78586	114010	GEN-BR	CAD PROTEIN (SEQ
<u>ID NO:2)</u>				
	3434		3408C>T	Silent
	4313		4287T>C	Silent
	4799		4773A>G	Silent
	5255		5229C>T	Silent
	5455		5429G>A	R1810Q
	5507		5481T>C	Silent
	5810		5784C>T	Silent
	6128		6102C>T	Silent
	6626		6600C>T	Silent
	6686		6660C>T	Silent
U09178	U09178	274270	GEN-HA	
Dihydropyrimidine	Dehydrogenase	(SEQ ID NO:3)		
	166		85T>C	C29R
	577		496A>G	M166V
	638		557A>G	Y186C
	1708		1627A>G	I543V
	3432		3351T>C	3'
	3682		3601C>T	3'
	3730		3649G>A	3'
	3925		3844A>G	3'
	3937		3856T>C	3'
U19720	U19720	600424	GEN-II	Folate
Transporter	(SLC19A1)	(SEQ ID NO:4)		
	175		80G>A	R27H
	341		246C>G	Silent
	791		696C>T	Silent
	1067		972G>A	Silent
	1337		1242C>A	Silent
	1997		1902T>C	3'
	2100	2005^2006insG		3'
	2582		2487T>G	3'

Applicant : Vincent P. Stan  
Serial No. :  
Filed : HEREWITH  
Page : 18

Attorney's Docket No.: 11926-015002

2617 2522C>T 3'  
2652 2557T>C 3'  
U92868 U92868 600424 GEN-LUK Homo sapiens reduced  
folate carrier (RFC1) gene, exons 1a, 1c and 1b (SEQ ID NO:5)  
431 431A>G Intron  
441 441A>G Intron  
498 498C>T Intron  
579 579G>C Intron  
599 599G>C Intron  
X02308 X02308 188350 GEN-KL Thymidylate  
synthetase (SEQ ID NO:6)  
1066 961T>C 3'  
1136 1031A>G 3'  
1497 1392T>A 3'  
D00517 D00517 188350 GEN-LUC Thymidylate  
synthase, promoter (SEQ ID NO:7)  
276 276C>T Intron  
321 321T>C Intron  
452 452G>A Intron  
457 457^insC Intron  
491 491C>A Intron  
533 533T>C Intron  
624 624A>C Intron  
639 639A>G Intron  
655 655T>C Intron  
D00596 D00596 188350 GEN-LUD Homo sapiens  
gene for thymidylate synthase, exons 1, 2, 3, 4, 5, 6, 7,  
complete cds (SEQ ID NO:8)  
701 701A>C Intron  
716 716A>G Intron  
732 732T>C Intron  
1293 1293A>G Intron  
1322 1322C>G Intron  
1379 1379T>C Intron  
1590 1590C>T Intron  
1688 1688C>G Intron  
2401 2401A>G Intron  
2429 2429G>A Intron  
2488 2488C>T Intron  
2594 2594G>T Intron  
2618 2618G>A Intron  
3083 3083G>A Intron  
3125 3125G>A Intron  
3212 3212C>T Intron  
3619 3619T>A Intron

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Applicant : Vincent P. Starck Jr.  
Serial No. :  
Filed : HEREWITH  
Page : 19

Attorney's Docket No.: 11926-015002

3635	3635G>A	Intron
4256	4256G>A	Intron
4898	4898A>G	Intron
5006	5006C>T	Intron
5062	5062G>A	Intron
5167	5167G>A	Intron
11069	11069A>G	Intron
11238	11238C>T	Intron
11293	11293T>G	Intron
11422	11422T>C	Intron
11686	11686C>T	Intron
12598	12598T>C	Intron
13171	13171T>C	Intron
13298	13298G>A	Intron
13645	13645T>C	Intron
13751	13751C>A	Intron
13782	13782T>C	Intron
13806	13806T>C	Intron
13813	13813T>C	Intron
14479	14479A>G	Intron
14546	14546^insT	Intron
14585	14585C>T	Intron
14729	14729G>A	Intron
14787	14787C>T	Intron
14795	14795G>A	Intron
15041	15041T>C	Intron
15343	15343G>A	Intron
15449	15449G>A	Intron
15502	15502G>A	Intron
15545	15545C>T	Intron
15589	15589A>G	Intron
15769	15769C>T	3'
15839	15839A>G	3'
16148	16148G>A	3'
16198	16198T>G	3'
16202	16202G>T	Intron

X59618	X59618	180390	GEN-M3	Ribonucleotide
reductase M2	polypeptide	(SEQ ID NO:9)		
128		(-67)G>A		5'
189		(-6)T>G		5'
524		330C>G	Silent	
1399		1205T>A		3'
1464		1270G>A		3'
1636		1442C>T		3'
1738		1544C>T		3'

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T04260.EE9650

Attorney's Docket No.: 11926-015002

	2259	2065T>C	3'
S72487	S72487	131222	GEN-3LD
phosphorylase, partial	<u>(SEQ ID NO:10)</u>		Thymidine
	183	19G>A	D7N
	483	319C>T	3'
	601	437G>C	3'
	1299	1135G>A	3'

M58602      M58602      131222      GEN-LUB      Thymidine  
phosphorylase, promoter and genomic (SEQ ID NO:11)

124	124C>T	3'
439	439G>A	3'
1044	1044^insCT	3'
1331	1331G>A	3'
1977	1977G>A	Intron
2149	2149G>A	Intron
2467	2467A>G	Intron
2634	2634C>G	Intron
2975	2975G>A	Intron
3116	3116G>T	Intron
3255	3255A>C	Intron
3344	3344T>C	Intron
4051	4051C>A	Intron
4782	4782G>A	Intron
5022	5022T>C	Intron
5266	5266G>A	Intron
5285	5285C>G	Intron
5438	5438T>A	Intron
5482	5482C>T	Intron
5629	5629G>A	Intron
5648	5648C>T	Intron
5731	5731G>A	Intron

M98045 M98045 136510 GEN-4C3 Homo sapiens  
folylpolyglutamate synthetase mRNA, complete cds (SEQ ID NO:12)

802	732C>T	Silent
1747	1677G>T	3'
1900	1830T>C	3'

U24253      U24253      136510      GEN-LUE      Human  
folylpolyglutamate synthetase (FPGS) gene, exons 5-11, and  
partial cds (SEQ ID NO:13)

1424	1424C>A	Intron
1649	1649G>A	Intron
2554	2554A>G	Intron

U24252      U24252      136510      GEN-LUF  
Folylpolyglutamate synthetase, promoter and exons 1-4 (SEQ ID  
NO:14)

1. 1997年12月31日	
流动资产	1,000,000
非流动资产	2,000,000
总资产	3,000,000
流动负债	1,500,000
非流动负债	500,000
所有者权益	1,000,000
负债和所有者权益	3,000,000
2. 1998年12月31日	
流动资产	1,200,000
非流动资产	2,200,000
总资产	3,400,000
流动负债	1,600,000
非流动负债	500,000
所有者权益	1,300,000
负债和所有者权益	3,400,000
3. 1999年12月31日	
流动资产	1,500,000
非流动资产	2,500,000
总资产	4,000,000
流动负债	1,800,000
非流动负债	500,000
所有者权益	1,700,000
负债和所有者权益	4,000,000
4. 2000年12月31日	
流动资产	1,800,000
非流动资产	2,800,000
总资产	4,600,000
流动负债	2,000,000
非流动负债	500,000
所有者权益	2,100,000
负债和所有者权益	4,600,000
5. 2001年12月31日	
流动资产	2,000,000
非流动资产	3,000,000
总资产	5,000,000
流动负债	2,200,000
非流动负债	500,000
所有者权益	2,300,000
负债和所有者权益	5,000,000
6. 2002年12月31日	
流动资产	2,200,000
非流动资产	3,200,000
总资产	5,400,000
流动负债	2,400,000
非流动负债	500,000
所有者权益	2,500,000
负债和所有者权益	5,400,000
7. 2003年12月31日	
流动资产	2,500,000
非流动资产	3,500,000
总资产	6,000,000
流动负债	2,600,000
非流动负债	500,000
所有者权益	2,900,000
负债和所有者权益	6,000,000
8. 2004年12月31日	
流动资产	2,800,000
非流动资产	3,800,000
总资产	6,600,000
流动负债	2,800,000
非流动负债	500,000
所有者权益	3,300,000
负债和所有者权益	6,600,000
9. 2005年12月31日	
流动资产	3,000,000
非流动资产	4,000,000
总资产	7,000,000
流动负债	3,000,000
非流动负债	500,000
所有者权益	3,500,000
负债和所有者权益	7,000,000
10. 2006年12月31日	
流动资产	3,200,000
非流动资产	4,200,000
总资产	7,400,000
流动负债	3,200,000
非流动负债	500,000
所有者权益	3,700,000
负债和所有者权益	7,400,000
11. 2007年12月31日	
流动资产	3,500,000
非流动资产	4,500,000
总资产	8,000,000
流动负债	3,500,000
非流动负债	500,000
所有者权益	4,000,000
负债和所有者权益	8,000,000
12. 2008年12月31日	
流动资产	3,800,000
非流动资产	4,800,000
总资产	8,600,000
流动负债	3,800,000
非流动负债	500,000
所有者权益	4,300,000
负债和所有者权益	8,600,000
13. 2009年12月31日	
流动资产	4,000,000
非流动资产	5,000,000
总资产	9,000,000
流动负债	4,000,000
非流动负债	500,000
所有者权益	4,500,000
负债和所有者权益	9,000,000
14. 2010年12月31日	
流动资产	4,200,000
非流动资产	5,200,000
总资产	9,400,000
流动负债	4,200,000
非流动负债	500,000
所有者权益	4,700,000
负债和所有者权益	9,400,000
15. 2011年12月31日	
流动资产	4,500,000
非流动资产	5,500,000
总资产	10,000,000
流动负债	4,500,000
非流动负债	500,000
所有者权益	5,000,000
负债和所有者权益	10,000,000
16. 2012年12月31日	
流动资产	4,800,000
非流动资产	5,800,000
总资产	10,600,000
流动负债	4,800,000
非流动负债	500,000
所有者权益	5,300,000
负债和所有者权益	10,600,000
17. 2013年12月31日	
流动资产	5,000,000
非流动资产	6,000,000
总资产	11,000,000
流动负债	5,000,000
非流动负债	500,000
所有者权益	5,500,000
负债和所有者权益	11,000,000
18. 2014年12月31日	
流动资产	

Applicant : Vincent P. Stan  
Serial No. :  
Filed : HEREWITH  
Page : 21

Attorney's Docket No.: 11926-015002

263	263A>G	Intron
266	266G>T	Intron
527	527C>G	Intron
1037	1037A>G	5'
1139	1139G>A	Intron
1217	1217C>T	Intron
1647	1647C>T	Intron
1955	1955G>A	Intron
2017	2017G>A	Intron
2037	2037G>A	Intron
2189	2189A>G	Intron
2282	2282C>T	Intron
2309	2309A>G	Intron

U09806 U09806 236250 GEN-4FZ Human  
methylenetetrahydrofolate reductase mRNA, partial cds (SEQ ID  
NO:15)

120	120T>C	Silent
464	464T>G	M155R
519	519C>T	Silent
668	668C>T	A223V
1059	1059T>C	Silent
1289	1289C>A	3'
1308	1308T>C	3'
1784	1784G>A	3'

AF061655 AF061655 123920 GEN-LUJ Cytidine  
deaminase, promoter (SEQ ID NO:16)

575	575T>C	Intron
648	648T>C	Intron
771	771G>C	Intron
883	883G>A	Intron
941	941^insC	5'
1051	1051A>C	K27Q

11926-015002